**Cardiac Membrane Potential**

* Cardiac PM is more negative inside and more positive outside
* CURRENT ALWAYS FOLLOWS + CHARGE
  + Outward current is + charge moving out or negative charge moving in
* Depolarization—PM becoming more positive
* Repolarization –PM returning to resting membrane potential (RMP)
* Hyperpolarizaiton—PM becoming more negative than RMP
  + Doesn't happen in normal physiology
* PM has high resistance and high capacitance (small change in charge will lead to very high potential difference)
* Ion channels allows PM to conduct ions
  + Conductance (G) = ability of a charged ion to cross the PM
  + g= # of channels \* open probability \* conductance of each channel
    - assume all voltage gated channels open on depolarization
* K+ is balanced by organic anion intracellularly and Na is balanced by Cl extracellularly
  + In K is highest—135
  + Outside Na is highest at 145
  + Ca is way higher outside the cell than inside
* Donan’s Equilibrium= where electrostatic and concentration charges are balanced across PM
  + Still have a concentration gradient but it is counteracted by electrical potential
* NERST EQUATION
  + Assumes 100% permeability of the ion
    - Membrane voltage = -61.5 log
    - K= -90 = reversal potential!
    - Na= +70
  + If membrane potential is < Nerst potentional then K always moves OUT!
  + K only moves in via Na-K pump
  + To account for permeability use the Goldman-Hodgkins-Katz equation
  + \*AT REST CARDIAC RMP = NERST POTENTIAL B/C AT REST CARDIAC MYOCYTE IS ONLY PERMEABLE TO K
* Hyperkalemia (worse than hypo): extracellular K > 5.5 mmol/L
  + Will have PM depol 🡪 can cause arrhythmias
* Hypokalemia: extracell K <3.5 mmol/L
  + Theoretical hyperpol but never hyperpol b/c cells will change permeability to K so it can’t leave and b/c Na will leak out
* To much or too little K in ECF induces cardiac depolarization
  + Easier to tx than hyper b/c just can give K

**Cardiac Action Potential Slow AP**

* AV and SA node are the only areas of the heart with SLOW AP’s
* Have a phase 4 automatic depolarization
  + Beating of the heart doesn't depend on nerves
  + This is why the heart will beat if you put it in a calcium solution
* Phase 0
  + Mainly slow channel (L-type) calcium channels
* Phase 3
  + Is due to a rapid K efflux by delayed rectifiers
* Phase 4
  + At the end of phase 3 the funny channel (HCN=hyperpolarization-activated cyclic-nt gated cation channel and NCX; voltage dep opens when the cell repol and closes when the cell depolar) open and cause Na influx that reverses the membrane potential and causes the cell to depol toward threshold
    - HCN & NCX open by cAMP
  + NCX (Na-Ca Exchanger)
    - Principle role of this exchanger is to drive OUT Ca that entered the cells druing preceding AP and systole
    - Charge follows Na
    - Driven by membrane voltage and intracellular calcium concentration myocyte
    - During the beginning of cardiac depol (right after phase 0) Vm (membrane voltage) becomes inside + and ↑ in [Na]i -🡪 this favors Na exit by the exchanger thus bringin in Ca (generating an outward current)
      * Heart also wants Ca right after depolarization for contracting
    - As AP progresses and [Ca]I rises, exchanger pushes out Ca (an inward current in generated)—during phase 2
      * This continues during cardiac diastole when the [Ca]I is ↑ and Vm is negative inside, Exchanger attract Na thus expelling Ca—generating an inward current
      * When myocytes are Ca overloaded enhanced Ca outflow generated inward current and leads to premature depolarization
      * \*\*cells always prioritize Na so if you inhibit Na/K ATPase (which moves Na out) then exchanger will favor getting rid of Na and taking in Ca 🡪 ↑ contractility but can cause Ca overload
    - Delayed Afterdepolarization
      * Systole—generates an outward current
      * Diastole—generates an inward current
      * When cardiac myocyte are Ca overloaded enhanced Ca outflow via the Ex generates inward current and leads to premature depolarizations (depolarization arrhythmias)
      * Caused by ↑ intracellular Ca
      * Delayed afterdepolarizations (DADs), begin during phase 4 - after repolarization is completed, but before another AP would normally occur. They are due to ↑ intracell [Ca], as might be seen with digoxin toxicity.
        + Overload is caused by ↓ ATP which leads to ↓ Na/K ATPase and SERCA
        + So ↓ Na/K ATPase would be ↑ [Na]intracellular so NCX would pump out Na and pump in Ca
        + Also the ↓ ATP would not allow SERCA to work which would ↓ Ca sequestration and ↑ intracellular calcium
        + The ↑ Ca would stimulate CICR which would also ↑ intracell Ca
        + The Ca overload would cause NCX to switch to pumping out Ca and In Na causing the delayed afterdepol)
    - Early Afterdepolarization
      * During cardiac systole, when Vm is inside positive the Ex repels Na, thus bringing in Ca- an **outward current is generated**
      * During cardiac diastole when the Vm is inside negative, Ex attracts Na thus expelling Ca- an **inward current is generated**
      * Prolonged phase 2 b/c compromised K channels (outward rectifiers)
        + Will see LQTS
      * If this happens before or during phase 3 it can lead to severe ventricular arrhythmias
      * Caused by ↑ intracellular Ca
      * Early afterdepolarizations (EADs) occur with abnormal depolarization during phase 2 or phase 3, and are caused by an increase in the frequency of abortive action potentials before normal repolarization is completed.
  + Activation of SNS through NE β-1 Receptors ↑ cAMP so rate of phase 4 depol would ↑
    - This is how SNS ↑ HR

**FAST AP**

* Phase 0
  + ↑ conductance of Na🡪 influc of Na causes depolarization at the end of phase 0 the Na channels are inactivated
  + ↑ the amplitude/slope of phase 0🡪 ↑ in conduction velocity (CV)
* Phase 1
  + Transient repolarization due to outward K current but channels are only open for a very short amount of time
* Phase 2
  + Plateau phase
  + L type calcium channels open and an influx of calcium while there is an efflux of K
  + Isoelectric phase
  + End of this phase Ca channels close
* Phase 3
  + Repolarization due to increased efflux of K
  + This causes inactivated Na channels to close so they can be reopened during the next AP
* Phase 4
  + Decreasing efflux of K b/c getting closer to RMP
  + No K current during phase 4 b/c its so close to NERST potential
  + Na channels are closed

**Conduction Velocity**

* Determinants
  + Rate of rise of phase 0
  + Amplitude of phase 0
  + Threshold of Na channel opening
  + Internal resistance of cardiac myocyte
    - AP in heart moves from one cell to the next via gap junctions—if these aren’t enough then the internal R is ↑ (this happens in the AV node—the IR is very high so conduction is difficult)
      * Fewer gap junctions in AV node
    - IR is also very high in cardiac fibrosis
    - AV node has 3 regions (AN, N, and NH)
      * AN and NH have both slow and fast AP
      * N has the highest IR & only has slow AP’s🡪 it is responsible for CONDUCTION DELAY--necessary so blood actually moves when heart pumps—that wouldn't happen if atria & ventricles contracted at the same time
  + Cardiac myocyte diameter
  + In cardiac ischemia some cell membranes are partially depolarized so not all the Na channels go from inactivated🡪 closed 🡪 this makes the slope of phase 0 less steep🡪 ↓ CV and AP travels slower 🡪 can lead to arrhythmias
    - To treat this you need to give something that opens K+ channels b/c you need repolarization –lidocaine does this
    - Also ischemia ↓ Na-K ATPase (b/c ↓ ATP In ischemic tissue) and that pump accounts for ~10mV so membrane is depol. At -80 so still inactivated Na channels—CV ↓
      * Na-K ATPase helps phase 3&4 relopolarization

**K+ Channel Rectification**

* Outward/ Delayed Rectifiers
  + Voltage gated K channels are closed at negative potentials and only open when the membrane depolarizes (phases 1🡪3)
  + They are instrumental in repol the membrane
  + These channels close when repolar or hyperpol
  + OPEN AFTER DEPOL
* Inward rectifiers
  + These close when membrane voltage is depolarized and open at negative membrane voltage (at rest or artificially hyperpol)
  + These maintain membrane voltage
  + These are open during phase 4
  + Closing of these channels makes AP possible: If they didn't then K+ going out would balance Na+ coming in
  + As a group CLOSE DURING PHASE 0

**Refractory Period**

* **Absolute refractory period**: inactivation of fast Na channels and Ca channels🡪 heart can’t be overstimulated
* **Effective refractory period**: slightlty longer than absolute RF
  + Period during which a conducted AP cannot be elicited
* **Relative Refractory period**: some of the Na channels recover to closed state and can be activated with higher than normal threshold. Resultant AP has ↓ CV (b/c have less Na channels out of inactivated state)
* **Supernormality**: threshold for activation is lower than for resting cardiac myocyte, the resultant AP is still slow

**Reentry Arrythmias**

* ↓ CV and disproportional refractory period promote circle movement and cardiac reentry arrhythemias
* The slow CV creates a unidirectional block—depolarization wave cant travel a certain way but can come back the other way
* 2 abnormalities
  + unidirectional block
  + ↓ effective refractory period
    - it is dependent on Na and Ca channels inactivated b/c PM didn't repol fast enough to close them.
    - Caused by overactivation of ANA to activate β1- receptors🡪 ↑ cAMP 🡪 PKA 🡪 Phosphorylate outward/delayed rectifiers🡪 ↑ their activity🡪 faster repolarization
  + ↓ CV
    - When ↓ CV after myocardial ischemia it activates the SNS b/c the BP drops 🡪 this also ↓ refractory period of all the cells both ischemic and nonischemic which is bad for the non-ischemic cells
    - This is why β blockers are so important in saving lives

**Autonomic Control on HR**

* Activation of SNS
  + ↑ cAMP🡪↑ steepness of phase 4/↑ in funny current
  + ↑ activity of Ca channels (both L and T type) which mediate phase 0 of slow AP (make it more steep)
  + ↑ activity of K channels 🡪 ↓ ↓ relative refractory period 🡪 ↑ HR
* Activation of PSNS
  + Activated Gi­ 🡪 ↓ cAMP🡪 phase 4 less steep
  + ↓ activity of Ca channels (both L and T type) which ↓ steepness of phase 0 in slow AP
  + ↑ activity of K channels 🡪 repolarization takes longer🡪 ↓ HR
  + Only works on SA and AV node—no regulation in ventricles.
  + If no PSNS HR would be 105 but PSNS suppresses the resting HR
  + 